The Rejections Under 35 U.S.C. § 102

Claims 1-13 and 21-25 are rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,504,074 to D'Amato et al. ("*D'Amato*"). Respectfully, this rejection is traversed.

D'Amato discloses methods of treating mammalian diseases characterized by abnormal cell mitosis using estradiol derivatives that bind tubulin, inhibit microtubule formation or exhibit anti-mitotic properties. See *D'Amato*, column 2, line 46- column 4, line 43. 2-methoxyestradiol is generally described as one of these estradiol derivatives, and its effects on cell division are presented in Tables 1 and 2. The effects on cell division by estradiol is also presented in Tables 1 and 2. *D'Amato* is completely silent with respect to 2-methoxyestradiol purity. Further, *D'Amato* does not describe how the 2-methoxyestradiol was made nor provide any information as to the source of the 2-methoxyestradiol employed in the experiments described therein. Therefore, it may be fairly concluded that the source was commercial and it cannot be assumed that the 2-methoxyestradiol was pure.

Claims 1-13 and 21-25 are rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,521,168 to Clark ("*Clark*"). Respectfully, this rejection is traversed.

Clark discloses using 2-methoxyestradiol for lowering intraocular pressure. As indicated in *Clark*, column 3, lines 45-46, "[t]he preferred estrogen metabolites are 2-methoxyestradiol and 2-hydroxyestradiol." *Clark* is completely silent with respect to 2-methoxyestradiol purity. Further, *Clark* does not describe how the 2-methoxyestradiol was made nor provide any information as to the source of the 2-methoxyestradiol employed in the experiments described therein. Therefore, it may be fairly concluded that the source was commercial and it cannot be assumed that the 2-methoxyestradiol was pure.

Claims 1-13 and 21-25 are rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,643,900 to Fotsis et al. ("*Fotsis*"). Respectfully, this rejection is traversed.

Fotsis discloses a method for the treatment of angiogenesis-sustained solid tumors in a mammal employing 2-methoxyestradiol. As indicated in the table at column 3, line 61-column 4, line 25, 4-methoxyestradiol, 2-hydroxyestradiol, and estradiol-17β were evaluated

along with 2-methoxyestradiol for their inhibitory effects of angiogenesis. *Fotsis* is completely silent with respect to 2-methoxyestradiol purity. Further, *Fotsis* does not describe how the 2-methoxyestradiol was made nor provide any information as to the source of the 2-methoxyestradiol employed in the experiments described therein. Therefore, it may be fairly concluded that the source was commercial and it cannot be assumed that the 2-methoxyestradiol was pure.

Claims 1-13 and 21-25 are rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 6,200,966 to Stewart et al. ("*Stewart*"). Respectfully, this rejection is traversed.

Stewart is directed to the use of 2-methoxyestradiol, 2-hydroxyestradiol, and 4-methyoxyestradiol, as well as other estradiol derivatives, to modulate airway remodeling by inhibiting inflammation and/or smooth muscle cell proliferation of the airway wall. As stated at column 10, lines 13-17, the source of 2-methoxyestradiol was lot 83H4065, Sigma, USA. Attached hereto as Exhibit "A" is a copy of the Certificate of Analysis for lot 83H4065. As indicated by the Certificate of Analysis, the purity as determined by HPLC of the 2-methoxyestradiol used by *Stewart* was only 98.0%.

As taught by the Applicants at page 2, lines 16-27, in the instant written description any therapeutic use of 2-methoxyestradiol in humans requires 2-methoxyestradiol having a high level of purity. In general, therapeutic agents are required to be substantially pure to avoid negative side effects of contaminants. In particular, since 2-methoxyestradiol has effects that are counteracted by estradiol and other estrogenic metabolites, in is crucial to have a 2-methoxyestradiol preparation substantially free of such contaminants. Effects that may be seen from contaminating estradiol, estrone, and 2-hydroxyestradiol include estrogenic effects such as feminization, endometrial proliferation, increased risk of uterine and breast cancer, developmental effects on sexual organs, inhibition of leukopoesis, and effects on hematopoetic cells. 4-hydroxyestradiol, 4-methoxyestradiol, and estradiol are known mutagens and carcinogens.

In contrast to the references, the claimed invention is directed to a composition comprising 2-methoxyestradiol having a purity greater than 99.5%. None of the cited references teach such a composition.

For a reference to qualify as prior art under 35 U.S.C. § 102, it is well established that the reference alone **must teach each and every element** of the claimed invention. See *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379, 213 U.S.P.Q. 81, 90 (Fed. Cir. 1986). (Emphasis added.) Missing elements may **not** be supplied by the knowledge of one skilled in the art or the disclosure of another reference. (Emphasis added.) See *Structural Rubber Prods. Co. v. Park Rubber Co.*, 749 F.2d 707, 716, 223 U.S.P.Q. 1264, 1271 (Fed. Cir. 1984). Since the *D'Amato*, *Clark*, *Fotsis*, and *Stewart* respectively fail to teach each and every element of the claimed invention, none of these references can anticipate the claimed invention. Accordingly, Applicants respectfully request that the rejections of Claims 1-13 and 21-25 under 35 U.S.C. § 102(b) and (e) be withdrawn.

The Rejections Under 35 U.S.C. § 103(a)

Claims 1-13 and 21-25 are rejected under 35 U.S.C. § 103(a) as being unpatentable over *D'Amato*, *Clark*, *Fotsis*, or *Stewart*. Respectfully, this rejection is traversed. *D'Amato*, *Clark*, *Fotsis*, or *Stewart* are discussed above and for brevity such discussion is incorporated here.

The U.S. Patent and Trademark Office ("PTO") states that "[e]ach of the cited prior art teaches the compound 2-methoxyestradiol and method(s) of using said compound in treatment of a disorder." Further, the PTO has taken the position that the rejected claims "differ from the references by reciting the compound has a purity of greater than 98%. However, purification of a compound to be utilized as a pharmaceutical agent would have been obvious to one having ordinary skill in the art at [the time of] the present invention. Therefore, the ordinary artisan in the art would have the reasonable expectation that the compound taught by the cited prior art references is in pure form."

Respectfully, the PTO's conclusion is not only unsupported, it is not correct with respect to the instant invention. Assuming *in arguendo* that the PTO's position that it is obvious

to purify compounds for pharmaceutical applications is correct, the degree of purity of the active compound and/or which impurities should be removed from the active compound is not obvious. As discussed by Applicants at page 2, lines 8-15, of their written description, "commercially available preparations of 2-methoxyestradiol are either less than 98% pure or contain undesirable steroid contaminants that are of concern for pharmaceutical uses." This is in sharp contrast to the PTO's position that "the ordinary artisan in the art would have the reasonable expectation that the compound taught by the cited prior art references is in pure form." The PTO has cited no reference to rebut Applicants' teaching. In support of Applicants' teaching and further rebutting the PTO's position is the attached Certificate of Analysis for lot 83H4065, which is the 2-methoxyestradiol employed by *Stewart*. As indicated by the Certificate of Analysis, the purity as determined by HPLC of the 2-methoxyestradiol was only 98.0%. Accordingly, the reference cited by the PTO refutes the PTO's position that "the ordinary artisan in the art would have the reasonable expectation that the compound taught by the cited prior art references is in pure form." (Emphasis added.) In fact, given the teachings of *Stewart*, such expectation is unreasonable.

Further, neither *D'Amato*, *Clark*, nor *Fotsis* state the degree of purity or the source of the 2-methoxyestradiol employed in the respective reference. Accordingly, since none of the experimental sections of these references discuss how the 2-methoxyestradiol was made, it may be reasonably concluded that commercially available 2-methoxyestradiol was employed, which, as Applicants teach, has a purity no greater than 98%. Even further, none of the cited references teach or suggest a 2-methoxyestradiol composition containing less than 0.03 % estradiol, 0.02% or less 2-hydroxyestradiol, 0.02% or less 4-hydroxyestradiol, 0.02% or less 4-methoxyestradiol, and less than 0.02% estrone, respectively. Actually, as discussed above, each of the references employs one or more of these compounds and fails to recognize them as impurities.

The determination of obviousness under 35 U.S.C. § 103 is a legal conclusion based on factual evidence. *Burlington Indus., Inc. v. Quigg*, 822 F.2d 1581, 1584, 3 U.S.P.Q.2d 1436, 1439 (Fed. Cir. 1987). The prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, must contain some suggestion or incentive that

would have motivated one of ordinary skill in the art to modify a reference or to combine references. *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988). Further, the prior art reference or combination of references **must teach or suggest all the limitations** of the claims. See *In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970). To support a conclusion of obviousness, "either the references must expressly or impliedly suggest the claimed combination or the [PTO] must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references." *Ex parte Clapp*, 227 U.S.P.Q. 972, 973 (Bd. Pat. App. & Int. 1985). In evaluating obviousness, the Federal Circuit made it very clear that one must look to see if "the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have had a reasonable likelihood of success viewed in light of the prior art." *In re Dow Chemical Co. v. American Cyanamid Co.*, 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988).

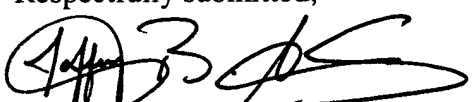
None of the references cited above teach or suggest a composition comprising 2-methoxyestradiol having a purity greater than 99.5%. Further, *Stewart* only employed a 98% pure 2-methoxyestradiol. *D'Amato*, *Clark*, and *Fotsis* are silent with respect to source and purity. Given Stewart, one of ordinary skill in the art could not reasonably conclude that 2-methoxyestradiol employed by *D'Amato*, *Clark*, and *Fotsis* was pure. Further, given the teachings of Stewart, one of ordinary skill in the art would conclude that 2-methoxyestradiol having a purity of 98% would be sufficient for pharmaceutical purposes. Since none of the cited references either alone or in combination teach or suggest all of the limitations of the claimed invention, the rejection under 35 U.S.C. § 103(a) is not proper. Accordingly, Applicants respectfully request that the rejection of Claims 1-13 and 21-25 under 35 U.S.C. § 103(a) be withdrawn.

CONCLUSION

The foregoing is submitted as a full and complete Response to the Office Action mailed August 14, 2001, and early and favorable reconsideration of the claims is requested.

Applicants respectfully assert that the rejections of the claims have been addressed and overcome. Applicants further assert that all claims are in a condition for allowance and request that a timely notice of allowance be issued. If the Examiner believes any informalities remain in the application which may be corrected by Examiner's Amendment, or there are any other issues which can be resolved by telephone interview, a telephone call to the undersigned attorney at (404) 949-2400 is respectfully solicited.

Respectfully submitted,



By: Jeffery B. Arnold
Reg. No. 39,540

KILPATRICK STOCKTON, LLP
Suite 2800
1100 Peachtree Street, N.E.
Atlanta, Georgia 30309
Phone: (404) 815-6500
Fax: (404) 815-6555
Our Docket: 43170-219662 (05213-0541)

"EXHIBIT A"

Product Number:**M6383**

Product Name:**2-Methoxyestradiol**

Product Information

Description / Pricing

Cert. of Analysis

Enter Lot No

Find

MSDS

Options

Print Preview

Bulk Quote

Ask A Scientist

SIGMA

Certificate of Analysis

TEST	SPECIFICATION	LOT {083H4065} RESULTS
Product Name	2-Methoxyestradiol	
Product Number	M6383	
CAS Number	362072	
Formula	$C_{19}H_{26}O_3$	
Formula Weight	302.4	
APPEARANCE	WHITE TO FAINT YELLOW POWDER	WHITE POWDER WITH A YELLOW CAST
SOLUBILITY	CLEAR COLORLESS TO FAINT YELLOW SOLUTION AT 10 MG/ML IN WARM ETHANOL	CLEAR FAINT YELLOW SOLUTION AT 5 MG PLUS 0.5 ML OF ETHANOL
IR SPECTRUM		CONSISTENT WITH STRUCTURE
SPECIFIC ROTATION		+105 DEG (C = 0.5 IN CHLOROFORM AT 20 DEG CENTIGRADE)
ULTRAVIOLET/VISIBLE SPECTRUM	EMM = 3.85 TO 4.00 AT LAMBDA MAX 287 TO 288 NM IN ETHANOL	EMM = 3.96 AT LAMBDA MAX 288 NM IN ETHANOL
PURITY BY THIN LAYER CHROMATOGRAPHY		>99.5%
PURITY BY HPLC	MINIMUM 98%	98.0%

Jeff Heiland, Manager
Analytical Services